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09/852,547	05/10/2001	David A. Sirbasku	1944-00800	6474

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EXAMINER
CANELLA, KAREN A

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/852,547	Applicant(s) Sirbasku
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *May 10, 2001* is/are a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election without traverse of Group I.

2. Claims 16 and 21-65 have been canceled. Claims 1-15 and 17-20 are pending and examined on the merits.

Specification

3. The disclosure is objected to because of the following informalities: the inclusion of blanks on pages 89, 90, 173 and 176.

Appropriate correction is required.

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications 60/203,314 and 60/208,348 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-15 and 17-20 of this application. Provisional application 60/229,071 was the earliest filed application to contemplate a method wherein an assay of secretory immunoglobulins in a patient would be indicative of an increased susceptibility to steroid hormone responsive cancers. Accordingly, the priority date of the instant application will be the filing date of the '071 provisional application, August 30, 2000.

Claim Rejections - 35 USC § 112

5.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-15 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite in the recitation of "predetermined standard". Without a clear description of the nature of the "predetermined standard in the claim, it is not possible to ascertain what would constitute a deficiency of said immunoglobulin inhibitor.

Claim 5 is rendered vague and indefinite in the recitation of "predetermined population", "predetermined amount of steroid hormone", "predetermined amount of steroid hormone free specimen" and "predetermined period of time". Claims 5 is also vague and indefinite in the recitation of: measuring the cell population in a control incubation mixture like said test mixture, except lacking "an amount" of said specimen. Without a recitation of a specific values or a range of values which define the population, amount of steroid hormone, amount of steroid hormone free specimen and a period of time, the metes and bounds of the claim cannot be determined.

The term "significant increase" and "significant lack of increase" in claim 5 is a relative term which renders the claim indefinite. The term "significant" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 8 recites "suitable in vitro cell culture assay". Without a specific limitation that would define the in vitro cell culture assay, the metes and bounds of the claim cannot be determined.

Claim 12 is rendered indefinite because it does not recite a step linking an action of the secretory immune system with the negative regulation of breast tissue proliferation

Claim 13 recites "receptor capable of mediating...". It is unclear if the receptor must actively mediate the steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth as part of the method or if the receptor need only possess the potential ability of being able to mediate said inhibition of cell growth. Claim 13 also recites "suitable in vitro cell culture assay" without defining or listing what constitutes said cell culture assay.

Claim 18 recites "if cells are stimulated by a preselected steroid hormone to proliferate in a suitable cell growth nutrient medium" without specifying an active method steps that would

follow in the case that the cells were stimulated and an active method step that would follow in the case that the cells were not stimulated.

The recitation of said loss or diminution in claim 19 does not have antecedent basis in the first condition of the claim. Claim 19 also recites "defined standard values" rendering the metes and bounds unable to be determined without means to establish a specific comparison between the specimen and the standard.

Claim 20 recites ERg. It is unclear what ERg encompasses, as estrogen-related receptor gamma is abbreviated as ERRg. For purpose of examination, ERg will be read as estrogen-related receptor gamma.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 10 is drawn to a method of detecting a genetic defeat in gene coding for poly-Ig receptor or Fcgamma receptor. Claim 11 is drawn to a method comprising the detection of a defective poly Ig receptor of Fc receptor. When given the broadest reasonable interpretation the claims are drawn to methods dependent on the identity of any possible "defective" poly Ig receptor or defective" Fc receptor. The claims are thus drawn to a genus of molecules encompassing mutant, truncated and otherwise variant poly-Ig or Fc receptor proteins. The claims do not limit the "defect" in terms of specific structural or specific functional characteristics., thus it is not possible to determine if a given protein is member of the claimed

genus The specification does not teach a representative number of defective poly-Ig receptors or defective Fc receptors that would be representative of the claimed genus. Because the genuses are highly variant, reliance on a description of the poly-Ig receptor or the Fcgamma receptor is insufficient to anticipate the claimed genus.

9. Claims 1-7, 12, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ (CCPA 1977)). Additionally the courts have determined that "...where a statement is , on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factor are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of

working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

Claim 7 is drawn to a method of detecting the loss of immunoglobulin regulation of steroid hormone responsive cell growth comprising assaying for inability of a mucosal epithelial cell to bind at least one immunoglobulin chosen from the group consisting of IgA, IgM and IGG1. Claim 12 is drawn to a method to aid in predicting susceptibility of a mammalian subject to development of breast cancer comprising detecting the loss or impairment of negative regulation of breast tissue proliferation by the secretory immune system. The specification teaches only that a secretory immunoglobulin which is present in human and non-human species interacts with hormone dependent cells to inhibit the growth of said cells. When given the broadest reasonable interpretation, the claim 7 encompasses any IgA, IgM or IgG1 including non-secretory antibodies; claim 12 encompasses secretory endogenous antibodies to exogenous or endogenous tumor antigens which were generated by the immune system including those antibodies which would react with a cell surface breast tumor antigen. The specification does not teach how to use the methods dependent on the multitude of antibodies encompassed by these claims. The scope of the claims must be commensurate with the enablement set forth. Given this lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to use the instant methods to the full scope of the claims.

Claims 1-6, 17 and 18 are drawn to method dependent on the identity of a steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth. The art teaches numerous serum factors that cause inhibition of steroid dependent cell growth. For instance, Ghosh et al (Indian Journal of Experimental Biology, Apr 2000, Vol. 38, pp. 313-322) teach that plasma IgA modulated the growth of Ehrlich ascites cells in vivo. Ehrlich ascites cells respond to estrogen as evidenced by the abstract of Das et al (Endocrinologia Japonica, 1976, Vol. 23, pp. 275-279) and are therefore estrogen dependent. Sonnenchein et al (J Steroid Biochemistry, 1996, Vol. 59, pp. 147-154) teach that estrocolyone obtained from serum inhibited

estrogen dependent cell growth. Tanji et al (Anticancer Research, Jul-Aug 2000, Vol. 20, pp. 2785-2790) describe two different proteins that mediated estrogen dependent inhibition of MCF-7 cells. These proteins appear to be normal constituents of serum, therefore it is reasonable to assume they will be detected in normal individuals not suffering from steroid dependent cell growth. The specification provides no guidance on ranges of said inhibitors that would be considered "normal" versus ranges or levels of said inhibitors that would be considered "abnormal" for any of these serum inhibitors. The specification teaches that secretory immunoglobulin binds to steroid responsive epithelial cells and inhibits steroid hormone cell growth. The specification bases the instant claims on the premise that measurement of said secretory immunoglobulins would then be diagnostic for inhibition of steroid responsive cell growth and that decreased levels of said immunoglobulins would then be indicative of decreased inhibition of said cell growth. However, it is known in the art that levels of IgA, the major secretory immunoglobulin, vary as a function of time of day, as well as within a year, and large variations between healthy subjects is documented (Garde et al, Clinical Chemistry, 2000, Vol. 46, pp. 551-559). The art also teaches that levels of secretory IgA is hormonally regulated in women and thus variable over the curse of a menstrual cycle (Gomez et al, Amer J Reproduc Immunol, 1993, Vol. 29, pp. 219-223). Given that the art teaches that the level of IgA varies with time in a healthy individual and also varies between individual subjects; and given the lack of teaching sin the specification regarding ranges or levels of secretory immunoglobulins that were indicative of normal individual or individuals having a steroid hormone responsive disease, one of skill in the art would not know how to use the claimed methods without undue experimenttion.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Krishnan et al (Prevention and Detection of Cancer, 1977, Nieburgs, Ed., pp. 449-453). Claim 8 is drawn in part to a method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising detecting a Fcgamma receptor in a mucosal epithelial cell, said receptor being capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable in vitro cell culture assay. Krishnan et al disclose a method for detecting Fc receptor activity in various breast carcinoma tissues by an agglutination assay with sheep erythrocytes sensitized with IgG. The method of Krishana et al is detecting Fcgamma as the agglutination agent is IgG sensitized erythrocytes. Further, it is inherent in the method of Krishnan et al that the Fc receptor on the breast carcinoma cells is the mediator of steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth as that is what is taught by the instant specification. The Fc receptor in breast carcinoma tissue would be capable of mediating steroid hormone reversible inhibition in a suitable cell clture assay.

Claim 8 is drawn in part to a method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising detecting a poly Ig receptor in a mucosal epithelial cell, said receptor being capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable in vitro cell culture assay. Hein et al discloses the detection of a poly-Ig receptor on an epithelial cell by means of a targeting molecule (page 9, line 3 to page 12, line 20). The poly Ig receptor would inherently have the capability of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable in vitro cell culture assay.

12. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Kimberly et al (WO 97/46715). Claim 9 is drawn to a method for detecting a gene coding for a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising detecting the presence of a Fcgamma receptor gene in a mucosal epithelial cell. Kimberly et al disclose a method for detecting the Fc gamma receptor in human epithelial cells comprising the detection of the Fc gamma gene. The Fc gamma receptor of an epithelial cell would inherently have the property of being a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth.

13. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by either of Becchis et al (Breast Cancer Research and Treatment, 1999, Vol. 54, pp. 101-107 or Markowitz et al (U.S. 5,866,323). Claim 19 is drawn in part to a method to aid in prognosis of a mammalian cancer patient comprising determining in a specimen of bodily fluid the lack of a cell growth inhibitory amount of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth, said loss or diminution being determine by comparison to defined standards , the presence of said condition being suggestive of at least some degree of reduced prognosis for said patient.

Beechis et al disclose a method of detecting the SHBG variant in plasma. Beechis et al disclose that the detection of said variant was correlated with the presence of ER+/PR+ tumors. Beechiis et al report that there was no difference in the amount of SHBG in the plasma, therefore, patients expressing the SHBP variant were not expressing the SHBP wild-type and therefore the teacings of Beechis fulfill the specific embodiments of claim 19 with regarding to the lack of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth, said ilacking nhibitor being wild-type SHBP. The method fulfills the specific embodiment of claim 19 with regard to the comparison to defined standard values as Figure 3 (page 104) indicates that purified SHBP was used as a control. The method of Beechis et al also fulfills the specific embodiment of aiding in the prognosis of a mammalian cancer patient as correlation with estrogen receptor

positive and/or progesterone receptor negative status of breast tumors is indicative of a better prognosis.

Claim 19 is drawn in part to a method to aid in prognosis of a mammalian cancer patient comprising determining in a specimen of neoplastic cells the loss or diminution of a TGF beta receptor or the gene encoding it

Markowitz et al discloses a method to aid in the prognosis of a mammalian cancer patient comprising determining in specimen of the quantity of functional TGF beta receptor subtype II (claims 1-4).

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

January 27, 2003